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TECHNICAL NOTE

Cardiopulmonary recirculation during hemodialysis

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Standard urea kinetic modeling (UKM) equations make the assumption that the blood entering the vascular access has the same composition as the blood leaving the systemic tissue compartment. While this assumption correctly describes the situation for a central venous access (Fig. 1A), such as a right atrial dialysis catheter, it is not adequate for the common peripheral access [1, 2]. The composition of the blood entering the access (c_{art}) during hemodialysis (HD) is different from the composition of the blood leaving the systemic tissue compartment (c_{ven}) (Fig. 1B). The manner in which the access and systemic circuits are connected has important, previously unrecognized consequences on the kinetic computation of urea distribution volume for blood-concentration-based UKM, and also affects the computation of access recirculation (AR). During HD, clearance of solute from the access loop dilutes the solute concentration of the blood entering the access. We have defined the 'long-loop' dilution effect on blood entering the access as 'cardiopulmonary recirculation' (CPR), because it is analogous to the 'short-loop' dilution effect which may take place through the vascular access ('access recirculation') [1]. It is the aim of this work to derive an analytical expression for CPR and to present a correction for the resulting reduction in HD efficiency in UKM equations.

Analysis

Constant volume, single-pool UKM equations define the removal of solute $[-V \times (dc_{ven}/dt)]$ from the systemic tissue compartment (V = urea distribution volume) as the product of the flow through the systemic tissue compartment (Q_V) multiplied by the concentration difference of the fluid leaving (c_{ven}) and entering (c_{art}) the tissue compartment:

$$-V \times \frac{dc_{ven}}{dt} = [c_{ven} - c_{art}] \times Q_V \qquad \text{(Eq. 1)}$$

The systemic (Q_V) and the access (Q_{Ac}) flows mix in the heart. When solute is cleared from the access flow during HD, this mixing reduces the solute concentration of the mixed arterial blood (Fig. 2). Since c_{art} is reduced, the concentration gradient which can be built up between the blood and the dialysate and therefore the concentration driving force to remove solute from the blood is also reduced. It is this systematic reduction of the available concentration at the access which reduces HD efficiency.

Removal of solute from the tissue compartment is equal to the removal of solute from the vascular access, where the effective concentration at the access is c_{art}, and not c_{ven}. Solute removal from the access is determined by access clearance (K_{Ac}) multiplied by mixed arterial concentration (c_{art}):

$$-V \times \frac{dc_{ven}}{dt} = K_{Ac} \times c_{art} \qquad \text{(Eq. 2)}$$

Access clearance (K_{Ac}) is dialyzer clearance (K_D) corrected for 'short loop' recirculation at the access site and, therefore, may be less than K_D. The equation for this correction factor (f_{Ac}) is described in the **Appendix**. Combination of Equations 1 and 2, and substitution to eliminate c_{art}, yields:

$$-\frac{dc_{ven}}{dt} = \frac{1}{1 + \frac{K_{Ac}}{Q_V}} \times c_{ven} \times \frac{K_{Ac}}{V} \qquad \text{(Eq. 3)}$$

This may be compared with the equation from classic UKM which does not take into account CPR:

$$-\frac{dc_{ven}}{dt} = c_{ven} \times \frac{K_{Ac}}{V} \qquad \text{(Eq. 3a)}$$

The corrected equation is linked to the classical equation by one additional term, f_{cp}, where

$$f_{cp} = \frac{c_{art}}{c_{ven}} = \frac{1}{1 + \frac{K_{Ac}}{Q_V}} \qquad \text{(Eq. 4)}$$

which can be thought of as a term correcting for the systematic effect of CPR. As long as $K_{Ac} > 0$, $f_{cp} < 1$. Usually f_{cp} is only slightly less than 1, but it can be a cause of significant reduction in HD efficiency.

Cardiac output (CO) is the sum of systemic flow (Q_V) and access flow (Q_{Ac}). Thus, Equation 4 can be rewritten in terms of familiar, measurable variables:

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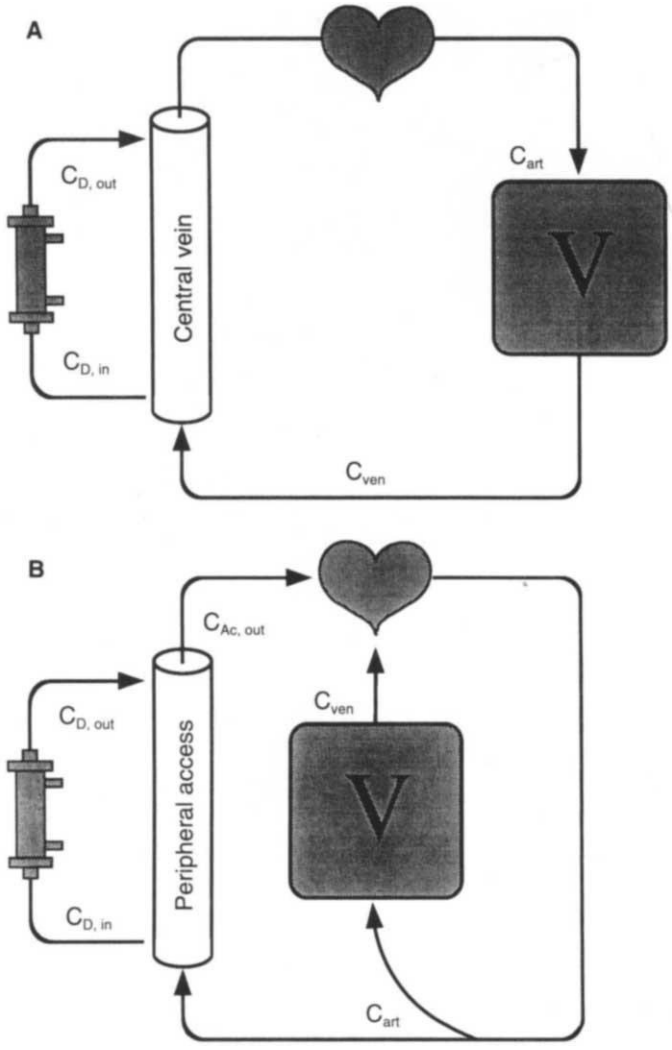

Fig. 1. *Access and systemic tissue circulation.* c_{ven} is the outflow concentration from the systemic tissue compartment. $c_{Ac,out}$ is the outflow concentration from the access and c_{art} is the inflow concentration into the systemic tissue compartment. $c_{D,in}$ and $c_{D,out}$ are dialyzer inflow and outflow concentrations, respectively. **A.** The composition of the blood entering the central vein is the same as the composition of the blood leaving the systemic tissue compartment (V). In terms of clearances, the central vein and the systemic tissue compartment are connected 'in series'. While AR is still possible with a right atrial dialysis catheter, CPR does not take place in this setting where all of the cardiac output is equilibrated with V. **B.** The heart (♥) is filled from the outflow of V, but it is also filled from the outflow of the peripheral access. A portion of the cardiac output perfuses the access, but the access flow rejoins and mixes with the remainder of the cardiac output only *after* having bypassed V. The composition of the mixed blood leaving the heart (c_{art}) and entering the access is different from the composition of the blood leaving the systemic tissue compartment (c_{ven}). In terms of clearances, the access and the systemic tissue compartment are connected 'in parallel' loops. The lung water compartment, which is connected in series with the right and left heart, is small when compared to the bulk of V so that its influence on arterial urea concentration (Eq. 4) is assumed to be negligible. During HD, when the extracorporeal circulation is connected to the access, dialyzer inflow concentration ($c_{D,in}$) may be influenced by recirculation of some part of cleared, dialyzer outflow blood ($c_{D,out}$). Recirculation through the access may occur because of unfavorable access flow conditions, whereas some degree of CPR is inherent to any circulation which contains a peripheral access.

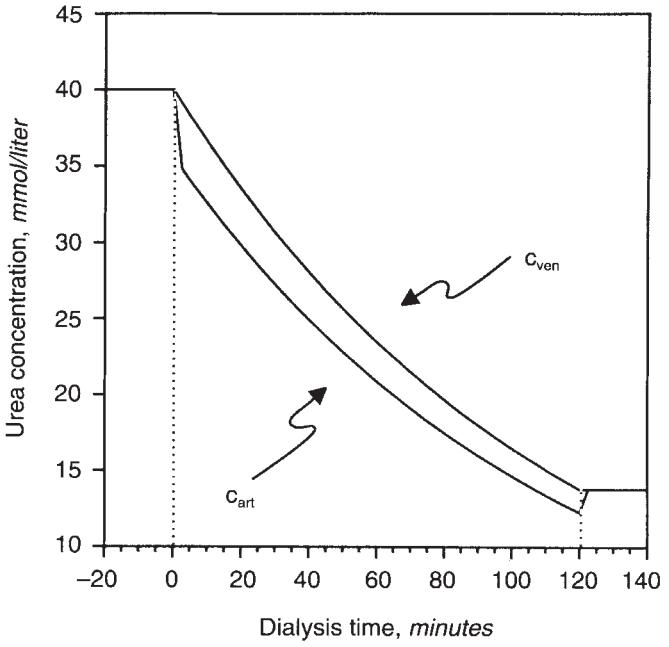

Fig. 2. *Urea concentration during HD.* The change of urea concentration (mmol/liter) in the tissue compartment (and in its equilibrated venous outflow, c_{ven}) is calculated for a model HD with constant values for access clearance K_{Ac} = 300 ml/min, systemic tissue compartment water V = 30 liters, cardiac output CO = 3000 ml/min and CPR Q_{Ac}/CO = 0.2. Predialysis plasma water urea concentration is assumed with $c_{ven,0}$ = 40 mmol/liter. Predialysis, venous and arterial blood water urea concentrations are equal. When HD starts and urea is cleared from the access, there is a rapid step-down in arterial blood water urea concentration (c_{art}). This sharp drop is due to the mixing of blood flows in the heart. c_{art} is a mixture of c_{ven} and $c_{Ac,out}$, weighted for the flow fractions ($c_{art} = c_{ven} \times Q_V/CO + c_{Ac,out} \times Q_{Ac}/CO$). With ongoing HD, both c_{ven} and c_{art} decrease as urea is cleared from the systemic tissue compartment. At the end of HD, when urea removal from the access stops, the dilution effect of CPR stops and there is a step-up in arterial blood water urea concentration. The step-up at the end is smaller than the step-down at the beginning of HD. This is due to the assumption that K_{Ac}, CO and CPR remain constant throughout HD, while $c_{ven,t}$ decreases. Because of the single pool assumption there is no increase in c_{ven} after the end of HD. A two compartment model would describe a postdialysis increase in c_{ven} that requires about 30 minutes to fully manifest [4]. [Urea concentration in equilibrated venous blood water at times = t is calculated from the solution of the equation corrected for CPR $c_{ven,t,corrected} = c_{ven,0} \times \exp -(t \times f_{cp} \times K_{Ac}/V)$, which is obtained from integration of Eq. 3. The correction factor f_{cp} is calculated from Eq. 4. The mixed arterial concentration entering the access (c_{art}) is calculated from $c_{art} = c_{ven} \times f_{cp}$ (Eq. 4)].

$$f_{cp} = \frac{1}{1 + \dfrac{K_{Ac}}{CO - Q_{Ac}}} \qquad \text{(Eq. 5)}$$

From Eq. 5 it follows that access clearance (K_{Ac}), cardiac output (CO) and access flow (Q_{Ac}) are the determinants of f_{cp}. A plot of f_{cp} versus K_{Ac} shows that, when the amount of CPR (Q_{Ac}/CO) is constant, f_{cp} decreases as access clearance (K_{Ac}) increases. The effect is more pronounced when cardiac output is low (Fig. 3). Normalization for cardiac output by plotting the function of f_{cp} versus K_{Ac}/CO leads to a single relation for constant CPR. The relation between f_{cp} and K_{Ac}/CO is only

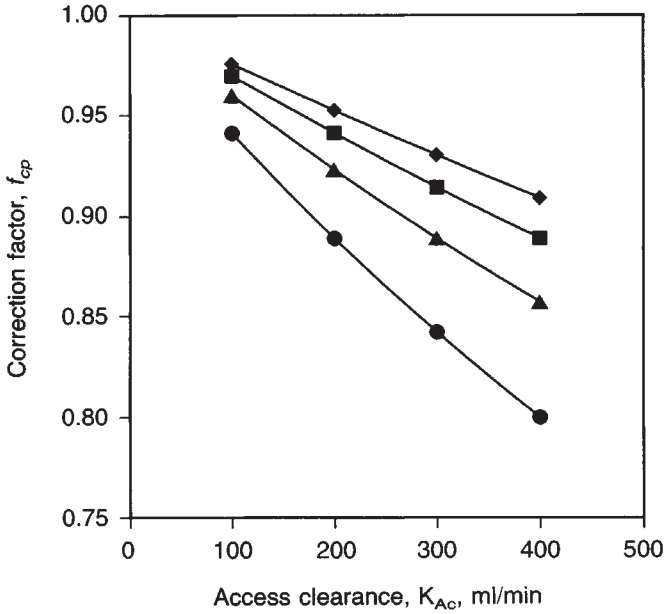

Fig. 3. *Relation between the cardiopulmonary correction factor (f_{cp}) and access clearance (K_{Ac}) (determined from Eq. 5).* Access clearances range from 100 to 400 ml/min. CPR is constant (Q_{Ac}/CO = 0.2). The relation is plotted for varying cardiac outputs: CO = 5 (◆), 4 (■), 3 (▲), and 2 liter/min (●).

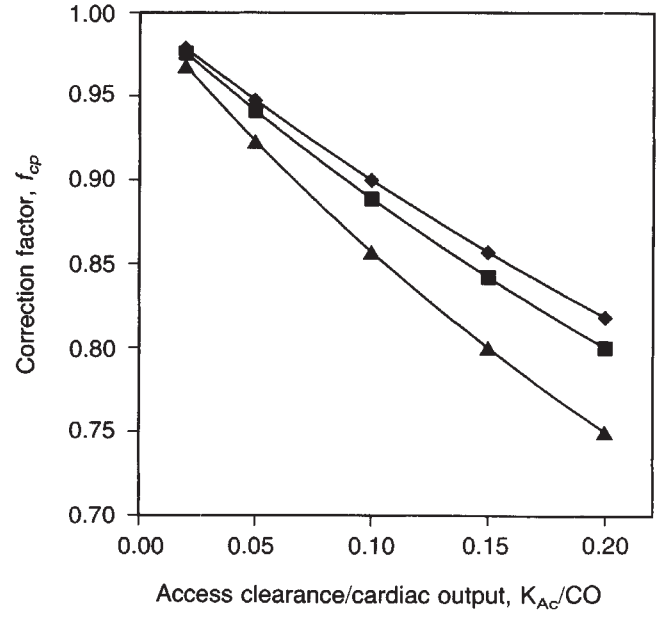

Fig. 4. *Relation between cardiopulmonary correction factor (f_{cp}) and the ratio of access clearance to cardiac output (K_{Ac}/CO) (determined from Eq. 5).* The range of access clearances and cardiac outputs is the same as in Fig. 3. The relation is plotted for varying CPR: Q_{Ac}/CO = 0.1 (◆), 0.2 (■), and 0.4 (▲).

modulated by the amount of CPR (Fig. 4). As CPR increases, f_{cp} will decrease for a given value of K_{Ac}/CO, resulting in a further decrease of HD efficiency. Normalizing for CPR by plotting f_{cp} as a function of K_{Ac}/Q_V instead of K_{Ac}/CO leads to

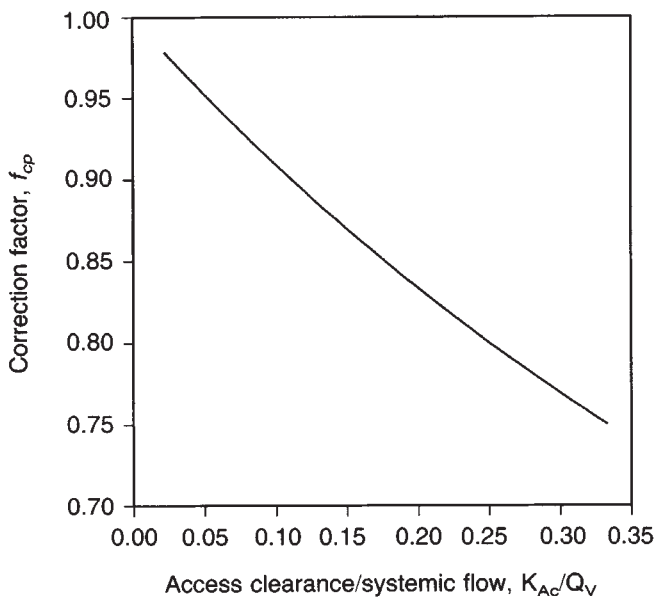

Fig. 5. *Relation between cardiopulmonary correction factor (f_{cp}), access clearance (K_{AC}) and systemic venous flow (Q_V) (determined from Eq. 4).* The data are the same in Fig. 4.

the single and generalized relationship expressed by Eq. 4 (Fig. 5).

Methods

The effect of CPR on dialyzer inlet urea concentrations was studied in six patients with loop grafts who had given informed consent. The graft was cannulated in the usual manner and extracorporeal blood flow was established while HD was in bypass. After an initial period of isolated ultrafiltration (170 ml/10 min), during which plasma urea concentrations in the extracorporeal circuit and in the cardiovascular system were allowed to equilibrate, HD was started (t = 0, Fig. 6). Ten minutes later, without changing the blood flow, the graft was occluded between the arterial and venous cannulation sites thus preventing possible AR [3]. Any immediate increase in arterial line urea concentration would have been related to previous AR. Two minutes later, HD was stopped for five minutes and the occlusion of the graft was released (t = 12, Fig. 6). HD was either completely stopped by disconnecting the extracorporeal circulation from the arterial and venous cannulas or significantly lowered by reducing Q_B to 50 ml/min ('stop-flow' technique [4]) and switching HD into bypass. Five minutes later, prescribed treatment was resumed. Blood samples from the arterial line were drawn every 20 to 60 seconds. Whole blood dialyzer clearance was determined by standard methods [4]. Cardiac output was measured by thoracic bioimpedance technique [5]. Urea concentrations are expressed as plasma urea concentrations (mmol/liter). Levels of significance were determined by the Wilcoxon signed-rank test.

Results

When HD was started, dialyzer inlet urea concentrations rapidly dropped after a lag phase of approximately 20 to 40 seconds (Fig. 6). The initial drop was more pronounced than the

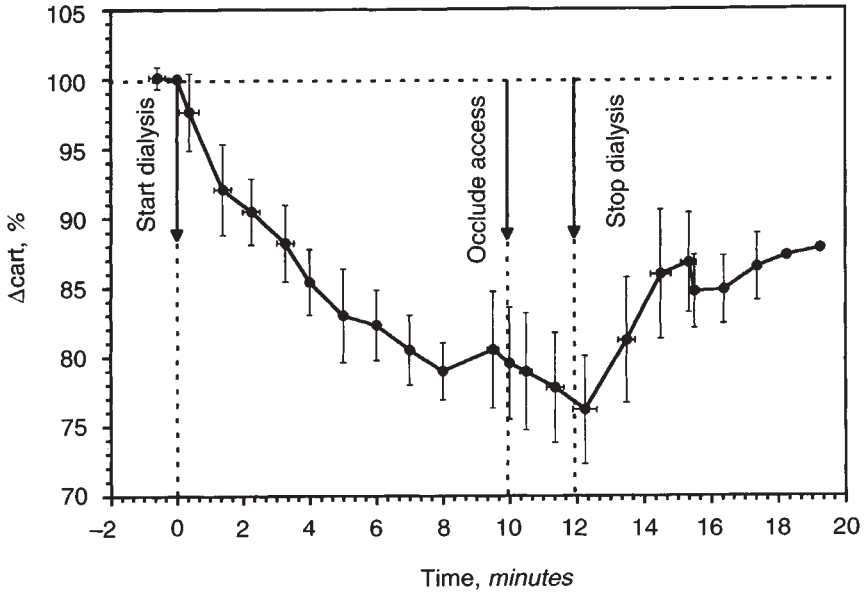

Fig. 6. *Relative decrease and increase of mean (±SD) dialyzer inlet urea concentration during HD and following the stop of HD.* Dialyzer inlet urea concentration was normalized for initial urea concentration (c_{art0}) and for body weight.

Table 1. Individual and mean (±SD) patient, treatment and stop-flow urea increase data

Patient	Body weight	Dry weight	CO	Q_B	K_D	Pre-dialysis urea	1 min increase	2 min increase	3 min increase	Theoretical increase
	kg		*liter/min*	*ml/min*		*mmol/liter*	%			
1	70.5	68	4.3	480	272	20.3	8	10	11	7.8
2	52.1	51	3.4	500	368	16.7	13	20	22	14.2
3	72.1	67.5	4.2	450	309	27.4	NA	9	10	9.1
4	60.8	59	5.9	500	305	20.1	NA	12	12	6.0
5	63.2	59	3.8	450	269	23.7	NA	7	12	9.0
6	55.1	55	4.6	500	327	28.1	3	10	14	8.6
Mean	62.3	59.9	4.4	480	308	22.7	8.0	11.3	13.5	9.1
SD	7.3	6.2	0.8	22	34	4.1	4.1	4.1	4.0	2.5

When HD is stopped, arterial line urea rapidly increases. The urea increase at 2 minutes was not different from the theoretical increase calculated from Eq. 5 (the one minute sample was not available (NA) in three experiments). Because AR was absent ($f_{Ac} = 0$) in these studies, $K_D = K_{Ac}$ (See Eq. A2).

drop observed during the following minutes of the HD treatment. When the graft was occluded, dialyzer inlet urea concentrations did not increase, demonstrating that AR was minimal in this group. However, when HD was stopped, dialyzer inlet urea concentrations rapidly increased by 8% after one minute, and by 11.3% after two minutes. The two minute value was not different from the theoretical increase of 9.1 ± 2.5% related to the reversal of CPR which was calculated from access clearance, cardiac output and an estimated access flow of 800 ml/min (Equations 4 and 5). The urea increase from two to three minutes was much less, but still significant ($P < 0.05$). Three minutes after stopping the blood flow, the urea increase was significantly higher than the theoretical estimate ($P < 0.05$; Table 1).

Discussion

In this paper we derive an analytical expression and present results for the substantial lowering of arterial line urea concentration by CPR during high efficiency HD. Our findings presented in this paper and data reported by us recently elsewhere [1] confirm and extend the hypotheses pertaining to CPR advanced by Sherman [2]. Before proceeding further, one point of confusion relating to both AR and CPR and HD must be clarified. Recirculation is a flow phenomenon that is not necessarily related to HD itself. AR may be present without HD, such as during HD bypass. CPR occurs continually in HD patients with a peripheral arterio-venous fistula or graft. It is HD that causes the effects of recirculation to become manifest by reducing the urea concentration of dialyzer inlet blood. Whenever HD is discontinued and clearance of urea from the extracorporeal circuit stops, recirculation of (dialyzer outlet) blood with low urea concentrations will cease and the effect of CPR will reverse, but the amount of CPR will be unchanged.

Our present data, combined with data obtained earlier from cold saline injection into the venous line lead to an interesting conclusion: the time constants for the reversal of AR and CPR effects after stopping HD are different. In one patient with AR, cold saline injected into the venous line began to appear at the arterial line within seconds after the injection [1]. In studies where AR was prevented from occurring, cold saline injected into the venous line appeared in the arterial blood line only after a considerable time delay (≈20 seconds) [1]. In other studies

where the dilution of saline injected into the venous blood line was used to determine cardiac output, the indicator appeared in the arterial blood line after a mean time lag of 17 seconds [6]. In the present studies, in which AR appeared to be minimal, an increase in urea concentration at the arterial blood line began 20 seconds after stopping HD (data not shown). The rapid increase in arterial line urea concentration continued for two minutes at which time experimental data matched the increase calculated from the theoretical relations presented in this paper. Subsequently, arterial line urea concentrations increased further, but at a slower rate. The delayed increase was most probably due to a true 'compartment effect' related to limited mass transfer across cells or alterations in regional blood flow [3].

At present we have not studied enough patients with and without AR to quantify the range of time constants for AR and CPR precisely. However, our observations regarding CPR are in accord with a theoretical time constant of 30 seconds for cross-stream mixing within a CPR loop (assuming a blood and lung water loop volume of 2 liters and a total cardiac output of 4 liter/min) [7]. With a theoretical time constant of 30 seconds for mixing and a delay of 20 seconds for cardiopulmonary transit, the effect of CPR on arterial line urea concentration would be 28% reversed at 30 seconds, 81% reversed at one minute, and 97% reversed at two minutes. These numbers are similar to the increases we observed (Fig. 6).

Our results as well as our computations suggest that CPR can result in a clinically important reduction in HD efficiency. In the patients we studied, mean access clearance and cardiac output was 308 ml/min and 4.4 liter/min, respectively (Table 1). The theoretical factor f_{cp} relating c_{art} to c_{ven} can be computed to be 0.92 (Eq. 5), but it may be 0.88 with high K_{Ac} and low CO, such as in patient 2. 'Effective clearance' (K) of the systemic tissue compartment, as we define it here, will only be $f_{cp} \times K_{Ac}$. This is different from the current definition of 'effective clearance' [8] which we now term 'access clearance' (K_{Ac}). In fact, effective clearance (K) is dialyzer clearance corrected for both AR and CPR (**Appendix**, Eq. A5). The relationships in Figures 3 to 5 point out clinical circumstances in which the CPR effect on HD efficiency will be magnified. These are:

(1.) High efficiency HD (because of high K_{Ac}),
(2.) Low cardiac output and,
(3.) High access blood flow relative to cardiac output, that is, high CPR (Q_{Ac}/CO).

As fluid is removed during dialysis and normal hemodynamic compensatory mechanisms come into play [9], cardiac output is reduced because of decreased filling, and the fraction of cardiac output flowing to the access may increase due to an increase in systemic vascular resistance. Both factors will enhance CPR related effects since systemic tissue flow ($Q_V = CO - Q_{Ac}$) will decrease under these conditions (Fig. 5).

What is the clinical importance of a 6 to 14% reduction in K_{Ac}? The effect of CPR has important implications both with respect to UKM and in the determination of AR.

Urea kinetic modeling

In variable volume, single-pool UKM equations, Kt/V, the amount of delivered dialysis, is determined primarily by the ratio of post-dialysis to pre-dialysis urea concentrations. Within a given post/pre-urea ratio, variations in effective clearance (K) or urea distribution volume (V) have only a minor effect on computed Kt/V. However, overestimation of K does result in a proportional error in the computation of V. In this study, failing to take into account the theoretical relation for CPR will result in a mean overestimation of K by 9.1% (min. 6%, max. 14.2%). Many have looked at the calculated V and its relation to estimated or measured total body water as one way of validating a given UKM technique. When urea removal is computed by total dialysate recovery, the computed value for V is often lower than the V computed from the measured dialyzer clearance [10, 11]. The effect of CPR will lower K (and also V) in UKM techniques where K is derived from dialyzer clearance measurements. The CPR effect, then, may partially explain some of the discrepancy in values for V computed using dialyzer clearance methods versus total dialysate recovery.

Table 2. CPR and computation of Kt/V: Effect of post-dialysis urea concentration

	Q_V	K_{Ac}	f_{cp}	Pre-urea	Post-urea	R	R-0.06	Kt/V
	liter/min	*ml/min*		*mmol/liter*				
(a)			1	40	13	0.325	0.265	1.33
(b)	3.6	300	0.92	40	14.1	0.353	0.293	1.23
(c)	2.4	300	0.89	40	14.6	0.365	0.305	1.19

Kt/V is calculated from [−ln(R-0.03-UF/W) [8] where R is the post- to pre-urea ratio, UF is the ultrafiltration volume and W is the body weight. The ratio UF/W is assumed to be 0.03. Pre-dialysis urea concentrations are the same in all three cases, whereas post-dialysis urea concentrations, after the reversal of CPR related effects, are different: (a) Since f_{cp} is 1, post-dialysis urea concentration reflects true systemic outflow concentration and Kt/V is 1.33. (b) The same post-dialysis urea concentration is measured. However, in this case, the sample was taken after only a short stop-flow period, insufficient for the reversal of CPR related dilution of arterial line urea concentration. If this patient's f_{cp} was 0.92, systemic outflow urea concentration would actually have been 14.1 mmol/liter so that delivered Kt/V was only 1.23. (c) The situation is similar in a smaller patient. Although arterial line post-dialysis urea was measured to be 13 mmol/liter, systemic outflow urea concentration was 14.6 mmol/liter and delivered Kt/V was only 1.19.

The CPR effect can also impact on computation of Kt/V. It is widely understood that at the end of HD the Q_B must be slowed for some time before drawing the post-dialysis blood sample. However, often the flow is reduced for only 15 to 30 seconds. Theoretically, the effects of CPR will not be completely reversed within such a short time period. As a result, arterial line samples obtained after only a short 'slow-flow' period will underestimate post-dialysis systemic tissue outflow urea concentrations. For a regular high efficiency HD treatment this will cause an overestimation of Kt/V by ≈8% (see example b) in Table 2).

Access recirculation

CPR also impacts importantly on the computation of AR. At least one group has suggested that AR, calculated by stop-flow method, increases as extracorporeal blood flow (and dialyzer clearance) increases [12]. In that study, blood was drawn after stopping HD for one minute. These results need to be reanalyzed in view of the relationships developed in the present paper. It must be emphasized that arterial line urea levels will always rise whenever the extracorporeal blood flow (and dialyzer clearance) is reduced. The increase is due to the reversal

not only of AR but also of CPR related effects. In the six patients described in the present report, AR was negligible, despite very high Q_B.

More detailed analysis of the time course of the urea increase, after slowing or stopping HD, will be required to precisely separate AR, CPR and compartment effects. Continuous measuring techniques capable of separating a fast indicator transit (≈5 seconds) through the short AR loop from the somewhat slower indicator transit (≈20 seconds) through the long CPR loop [1, 13] may prove to be helpful. Thermodilution as well as optical techniques are especially promising. However, to date only qualitative assessments of true AR have been reported [14–16].

While the separate determination of cardiopulmonary and access effects is difficult, determination of their joint effect is more easily achieved. Since dialyzer and access clearances are zero during HD bypass or during stopped extracorporeal blood flow there is no dilution of c_{ven}, and the correction factor for the joint effect of CPR and AR, which we call f_{sum}, will become 1 (see Equations A1 through A8 in the **Appendix**). We can compute f_{sum} during dialysis (Eq. 6, below) as the ratio of arterial line urea concentrations during HD and after reversal of AR and CPR effects (best taken after a 2 min waiting period):

$$f_{sum} = \frac{c_{Din}\ (\text{during HD})}{c_{Din}\ (\text{during bypass or stop-flow})} \qquad \text{(Eq. 6)}$$

In summary, our results emphasize a previously underrecognized effect of CPR on arterial line urea concentration when a peripheral arterio-venous access is used. The CPR effect can lead to an overestimation of both urea distribution volume (V) and 'modeled' Kt/V value. Also, the CPR effect can lead to overestimation of AR. In order to correct for CPR related effects, timing of blood sample collection will have to consider the results presented in this paper.

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Appendix

Access recirculation ($R_{Ac} = Q_{AR}/Q_B$), the ratio of access recirculation flow (Q_{AR}) to extracorporeal blood flow (Q_B), reduces the efficiency of dialyzer clearance (K_D). The factor (f_{Ac}) to correct dialyzer clearance for access recirculation has been derived previously [17].

$$f_{Ac} = \frac{1 - R_{Ac}}{1 - R_{Ac} \times \left(1 - \frac{K_D}{Q_B}\right)} \qquad \text{(Eq. A1)}$$

Therefore, with

$$K_{Ac} = K_D \times f_{Ac} \qquad \text{(Eq. A2)}$$

Eq. 3 (see **Analysis**) may be transformed into

$$-\frac{dc_{ven}}{dt} = \frac{1}{1 + \frac{K_D \times f_{Ac}}{CO - Q_{Ac}}} \times f_{Ac} \times c_{ven} \times \frac{K_D}{V} \qquad \text{(Eq. A3)}$$

The factor (f_{sum}) correcting for the joint effect of both AR and CPR is given by:

$$f_{sum} = \frac{1}{1 + \frac{K_D \times f_{Ac}}{CO - Q_{Ac}}} \times f_{Ac} \qquad \text{(Eq. A4)}$$

which also relates dialyzer clearance to effective clearance (K):

$$K = f_{sum} \times K_D \qquad \text{(Eq. A5)}$$

The removal of solute from the tissue compartment equals the removal of solute from the extracorporeal circulation. The latter is determined by dialyzer clearance (K_D) multiplied by the solute concentration at the dialyzer inflow (c_{Din}):

$$-V \times \frac{dc_{ven}}{dt} = K_D \times c_{Din} \qquad \text{(Eq. A6)}$$

Combining Eqs. A3 and A6, eliminating $[(K_D/V) \times (dc_{ven}/dt)]$, substituting f_{sum} from Eq. A4, and rearranging for f_{sum}, yields:

$$f_{sum} = \frac{c_{Din}}{c_{ven}} \qquad \text{(Eq. A7)}$$

which relates the correction factor f_{sum} to the ratio of the solute concentrations entering the dialyzer and leaving systemic tissue compartments. f_{sum} describes the effective fraction of c_{ven} which enters the dialyzer.

During HD bypass or stopped extracorporeal blood flow, $K_D = 0$ and therefore $f_{Ac} = 1$ (Eq. A1) and $f_{sum} = 1$ (Eq. A4). It follows from Eq. A7 that

$$\lim_{K_D \to 0} c_{Din} = c_{ven} \qquad \text{(Eq. A8)}$$

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